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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/538,248	03/29/2000	David A. Cheresh	TSRI-651.3	6166

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EXAMINER	
PROUTY, REBECCA E	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/02/2002 13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/538,248	Applicant(s) Cheresh et al.
	Examiner Rebecca Prouty	Art Unit 1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on *Jul 8, 2002*.

2a) [X] This action is **FINAL**. 2b) [ ] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *1-31* is/are pending in the application.

4a) Of the above, claim(s) *5-15 and 21-31* is/are withdrawn from consideration.

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) *1-4 and 16-20* is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are a) [ ] accepted or b) [ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) [ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) [ ] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____.
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) [ ] The translation of the foreign language provisional application has been received.

15) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [ ] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s).
4) [ ] Interview Summary (PTO-413) Paper No(s).
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other:

Claims 1-31 are still at issue and are present for examination.

Applicants' arguments filed on 7-8-02, paper No. 12, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 5-15 and 21-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction/election requirement in Paper No. 9.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and

potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 and 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of van Bruggen et al., Aiello et al. (US Patent 6,284,751) or Jirousek et al. (US Patent 6,093,740) in view of Munshi et al. The rejection is explained in the previous Office Action.

Applicants argue that none of van Bruggen et al., Aiello et al. or Jirousek et al teach a Src kinase inhibitor for the treatment of vascular edema and Munshi et al. do not teach a relationship of Src kinases to VEGF signaling with respect to vascular edema and thus, given the complexity of VEGF signaling pathways, one of ordinary skill in the art would have found it merely found it obvious to try to inhibit vascular edema with a Src kinase inhibitor such as PP1 or PP2.

This is not persuasive because Munshi et al. clearly show that PP1 inhibited a number of different downstream effects of VEGF stimulation but had no effect on VEGF-receptor autophosphorylation. Thus the ordinary skilled artisan would reasonably conclude that Src kinase activation is a early event in the VEGF signaling pathway. Furthermore, as Src is well known in the art to be expressed in all cell types, the skilled artisan would expect it to be involved in the signaling pathways in other

cells beyond the KS cells of Munshi et al. It should be noted that Munshi in fact explicitly concludes that Src kinase is an early mediator that links VEGF signals (i.e., VEGF receptor autophosphorylation) to downstream effectors (see page 1169). As such one of skill in the art would have reasonably expected the activation of Src kinase by VEGF to play a role in other known downstream effects of VEGF. van Bruggen et al., Aiello et al. and Jirousek et al. all clearly identify vascular edema as a downstream effect of VEGF and express a need in the art for other inhibitors of the VEGF signaling pathway. Therefore, it would have been obvious to one of ordinary skill in the art to substitute PP1 for the VEGF inhibitor of van Bruggen et al., Aiello et al., or Jirousek et al. as Munshi et al. teach that PP1 is another inhibitor of VEGF signaling and thus would be expected to have similar therapeutic effects as the VEGF inhibitors of van Bruggen et al., Aiello et al., or Jirousek et al.

Claims 1-4 and 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of van Bruggen et al., Aiello et al. (US Patent 6,284,751) or Jirousek et al. (US Patent 6,093,740) in view of Hanke et al. and either of He et al. or Cooke et al. The rejection is explained in the previous Office Action.

Applicants argue that none of van Bruggen et al., Aiello et al. or Jirousek et al teach a Src kinase inhibitor for the treatment of vascular edema, that Hanke et al. teach that inhibition of protein tyrosine kinases is an unpredictable art and that the effectiveness of PP1 and PP2 against Src family kinases is variable and not predictable and He et al. and Cooke et al. do not teach a relationship of Src kinases to VEGF signaling with respect to vascular edema and thus, given the complexity of VEGF signaling pathways, one of ordinary skill in the art would have found it merely found it obvious to try to inhibit vascular edema with a Src kinase inhibitor such as PP1 or PP2.

This is not persuasive for several reason. With regards to applicants comments regarding inhibition of protein tyrosine kinases being an unpredictable art and that the effectiveness of PP1 and PP2 against Src family kinases is variable and not predictable, PP1 was specifically shown to inhibit Src by Hanke et al. (see page 698) and PP2 is specifically disclosed by both He et al. and Cooke et al. to inhibit Src. As such applicants statements are not persuasive. Furthermore, applicants arguments that He et al. and Cooke et al. do not teach a relationship of Src kinases to VEGF signaling with respect to vascular edema is not persuasive as He et al. specifically state that "The effects

of VEGF in stimulating angiogenesis **and increasing vascular permeability** also require NOS activity", i.e., increasing vascular permeability also requires NO production. As He et al. show that PP2 blocks VEGF-induced NO production in cells, he has explicitly connected PP2 inhibition and vascular permeability. Cooke et al. also make a connection between vascular permeability and PP2. Cooke et al. disclose that VE-cadherin is a protein that mediates cell-cell adhesion of endothelial cells and is involved in regulating vascular permeability, that VEGF induces tyrosine phosphorylation of VE-cadherin and that PP2 inhibits this phosphorylation. As such one would reasonably conclude that the phosphorylation of VE-cadherin is the effector for the increased vascular permeability signaled by VEGF and PP2 would inhibit vascular permeability.

Claims 1-4 and 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of van Bruggen et al., Aiello et al. (US Patent 6,284,751) or Jirousek et al. (US Patent 6,093,740) in view of Hanke et al. and Eliceiri et al. (1998). The rejection is explained in the previous Office Action.

Applicants argue that none of van Bruggen et al., Aiello et al. or Jirousek et al teach a Src kinase inhibitor for the treatment of vascular edema and Eliceiri et al. do not teach a

relationship of Src kinases to VEGF signaling with respect to vascular edema and thus, given the complexity of VEGF signaling pathways, one of ordinary skill in the art would have found it merely found it obvious to try to inhibit vascular edema with a Src kinase inhibitor such as PP1 or PP2.

This is not persuasive as Src is well known in the art to be expressed in all cell types, the skilled artisan would have reasonably expected the activation of Src kinase by VEGF to play a role in other known downstream effects of VEGF. van Bruggen et al., Aiello et al. and Jirousek et al. all clearly identify vascular edema as a downstream effect of VEGF and express a need in the art for other inhibitors of the VEGF signaling pathway. Therefore, it would have been obvious to one of ordinary skill in the art to substitute PP1 for the VEGF inhibitor of van Bruggen et al., Aiello et al., or Jirousek et al. as Eliceiri et al. teach that Src Kinase activity is required for VEGF signaling pathways and Hanke et al. teach that PP1 and PP2 inhibit Src kinase activity and thus PP1 and PP2 would be expected to have similar therapeutic effects as the VEGF inhibitors of van Bruggen et al., Aiello et al., or Jirousek et al.

Applicants also argue that the entire subject matter disclosed by Eliceiri et al. was disclosed in the parent application and thus applicant should be granted the priority

date of the parent application for this subject matter. This is not persuasive because it is not particular subject matter that is granted a priority date, but a particular claim. **All** of what is claimed in any particular claim must find support in a parent application in order for the claim to be granted benefit of the parent application filing date. Each of the examined claims includes limitations that are **not** supported in the parent application as previously discussed (i.e., the current claims would have been rejected as including new matter if introduced in the parent application). As such none of the instant claims have been granted the benefit of the parent application filing date.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the

statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (703) 308-4000. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Rebecca Prouty
Primary Examiner
Art Unit 1652